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Questions and answers

Withdrawal of the application for a change to the marketing authorisation for Adempas (riociguat)

On 11 August 2016, Bayer Pharma AG officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a change to the marketing authorisation for Adempas, in the treatment of pulmonary arterial hypertension.

What is Adempas?

Adempas is a medicine that contains the active substance riociguat. It is available as tablets (0.5, 1, 1.5, 2 and 2.5 mg).

Adempas has been authorised since March 2014. It is already used to increase the ability to carry out physical activity in adults with the following forms of pulmonary hypertension (high blood pressure in the blood vessels of the lungs):

- Chronic thromboembolic pulmonary hypertension (CTEPH, where the blood vessels in the lungs are blocked or narrowed by blood clots). Adempas is used to treat patients with CTEPH who cannot be operated on, or in whom CTEPH remains or returns after surgery.
- Pulmonary arterial hypertension (PAH, where the walls of the blood vessels of the lungs are thickened and the vessels become narrowed). Adempas can be used on its own or in combination with other medicines for PAH called 'endothelin receptor antagonists'.

Adempas is used in patients with functional class II to III CTEPH or PAH. The 'class' reflects the severity of the disease: 'class II' involves slight limitation of physical activity while 'class III' involves marked limitation of physical activity.

For PAH, Adempas was found to be effective in patients with idiopathic (of unknown cause) or inherited PAH or PAH caused by connective tissue disease.

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What was Adempas expected to be used for?

Adempas was also expected to be used specifically for the treatment of adults with PAH associated with congenital heart disease (heart disease present at birth).

Adempas was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 20 December 2007 for the treatment of PAH including CTEPH. This orphan designation covers PAH associated with congenital heart disease (PAH-CHD). Further information on the orphan designation can be found here.

How is Adempas expected to work?

In PAH-CHD, Adempas is expected to work in the same way as it does in its existing indications. The active substance in Adempas, riociguat, stimulates an enzyme called 'soluble guanylate cyclase' in the blood vessels of the lungs, which causes the blood vessels to relax and widen. This helps to lower the blood pressure in the lungs and improve symptoms of PAH.

What did the company present to support its application?

The company did not conduct any new studies. It provided an analysis of results in patients with PAH-CHD taken from the main studies in PAH patients which compared Adempas with placebo (a dummy treatment). About 8% of patients in the main studies had PAH-CHD. The main measure of effectiveness was the increase in the distance patients could walk in 6 minutes (a way of measuring exercise capacity).

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions to be answered. The company had not yet responded to the questions at the time of the withdrawal.

What was the recommendation of the CHMP at that time?

Based on the review of the data, at the time of the withdrawal, the CHMP had some concerns. However, the CHMP thought that the company could have addressed these concerns and was of the provisional opinion that Adempas could have been approved for the treatment of PAH-CHD.

The CHMP's main concern was that because the main study had not been set up to investigate Adempas specifically in patients with PAH-CHD, the results were not suitable for determining the effectiveness of the medicine in this subgroup of patients. The CHMP was also concerned that few patients with PAH-CHD were investigated and that the analysis of side effects in PAH-CHD patients was not sufficiently robust.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the company had not fully addressed their concerns and the benefit and risks of Adempas in the specific treatment of PAH-CHD had not been demonstrated satisfactorily.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that the withdrawal is based on the revised product development strategy for the product.

The withdrawal letter is available here.

What consequences does this withdrawal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that this withdrawal has no impact on patients participating in ongoing clinical trials or compassionate use programmes with Adempas.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

What is happening with Adempas for the treatment of other diseases?

There are no consequences on the use of Adempas in its authorised indications.

The full European Public Assessment Report for Adempas can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.